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Reverse genetics

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Some of the characteristics of schizophrenia may be understood from the point of view of excessive incentive learning (IL). IL is the acquisition by previously neutral stimuli of an increased ability to elicit approach and other responses. Dopamine (DA) plays a key role in the establishment and maintenance of IL. DA D1-like or D2 receptor antagonists block the acquisition of IL. In animals that have already acquired IL, acquisition-blocking doses of these drugs do not initially block expression; with continued testing whereas in the drug state, IL gradually is lost. D3 receptor antagonists appear to have a different profile, blocking expression of IL at doses that fail to block acquisition. Thus, the D3 partial agonist BP 897 blocked expression but not establishment of conditioned activity or place preference based on amphetamine. BP 897 or the selective D3 receptor antagonist SB-277011A attenuated conditioned suppression of lever pressing produced by a stimulus previously paired with electric shock but failed to block establishment of conditioning when given during stimulus-shock pairings. The selective D3 receptor antagonist ABT-127 blocked expression of conditioned activity based on cocaine at a dose that failed to block acquisition. These effects were doubly dissociated from those of the D2-preferring antagonist haloperidol that blocked acquisition at a dose that failed to block expression. A number of signaling molecules including PKA, ERK1/2, p38, protein kinase C** and calcineurin in the nucleus accumbens have been implicated in IL. DA may produce IL by modifying glutamatergic α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. How D1 and D2 receptors interact to produce this learning remains to be worked out. Results suggest a complex interaction of DA, acting at a number of its receptor subtypes, with glutamatergic synapses mediated by cascades of signaling molecules to produce and maintain IL. A better understanding of these mechanisms will point the way towards the development of new pharmacological tools for the treatment of schizophrenia (funded by NSERC).

SYMPOSIUM 2: FORWARD AND REVERSE GENETIC APPROACHES TO REWARD AND ADDICTION, COMBINED WITH: GENETICS IN DRUG ADDICTION

S4 MICROARRAY STUDIES ON DRUG-INDUCED CHANGES IN GENE EXPRESSION

M.J. Kreek

Abstract not provided

S5 REVERSE GENETICS: COCAINE'S MECHANISMS SCRUTINIZED USING KNOCKOUT AND MUTANT RATS DERIVED FROM ENU-DRIVEN TARGET-SELECTED MUTAGENESIS

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The treatment of cocaine addiction is hampered by a lack of effective pharmacological therapies. Over decades, enormous progress has been made in the understanding of cocaine's neurobiological mechanism. However, because of the interactions between systems on which cocaine impinges, the precise role of individual systems has been difficult to delineate. Yet, this information may be useful to identify targets for pharmacological therapies. Recent advances in genetics have provided a variety of tools to manipulate neurotransmitter systems. For example, knockout mice have provided important insights into cocaine's neurobiological mechanisms. Because rats are traditionally used in addiction research, the use of knockout mice required several adaptations in behavioural set-ups, which were sometimes complicated by the small size and the differences in cognitive capabilities of mice as compared with rats. Several attempts have been made to generate knockout rats, but failed because of the lack of rat embryonic stem cells that are required for the homologous recombination approach. To overcome this limitation, we applied ENU-driven target-selected mutagenesis in rats. ENU induces point mutations that can result in premature stop codons that interrupt the translation of mRNA into a proper protein, or in amino acid changes that may affect protein function. We have identified a premature stop codon in the rat serotonin (5-HT) transporter (*SERT*) gene and studying the resulting *SERT* knockout rat in several behavioural models unmasked the inhibitory role of 5-HT in cocaine's rewarding and motivational properties, and the contribution of compensatory adaptations in 5-HT_{1A} receptor function. Other potential interesting knockout rats in drug addiction research are the melanin-concentrating hormone and opioid-like receptor knockout rats. Finally, preliminary findings point out that a mutant rat with an amino acid change in the dopamine D1 receptor is highly interesting in cocaine addiction research, especially because of a lack of selective dopamine D1 ligands.